Attorney Docket No.:

ISIS-5028

Serial No.:

10/080,979

Page 2

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently amended) A method of modulating the expression of a nucleic acid in the hepatic system of a mammal, comprising the step of:

administering to said mammal an <u>antisense</u> oligonucleotide which hybridizes to said nucleic acid to modulate the expression of said nucleic acid,

wherein said oligonucleotide has at least two sterol moieties covalently bonded thereto and is cleared from the circulation at approximately the same rate as a second oligonucleotide wherein said second oligonucleotide has no sterol moieties covalently bonded thereto.

- 2. (Canceled)
- 3. (Original) The method of claim 1, wherein at least one of said sterol moieties is a cholesteryl moiety.
- 4. (Original) The method of claim 1, wherein said oligonucleotide comprises two cholesteryl moieties.
- 5. (Original) The method of claim 1, wherein said sterol moieties are bound at the 2'-O, 3'-O or 5'-O positions of said oligonucleotide.
- 6. (Currently amended) A method of preferentially targeting an antisense oligonucleotide to liver cells in a mammal, comprising the steps of:

covalently bonding said oligonucleotide to at least two sterol moieties to form a sterol-oligonucleotide conjugate; and

ISIS PATENT DEPT

Attorney Docket No.:

ISIS-5028

Serial No.:

10/080,979

Page 3

administering said sterol-oligonucleotide conjugate to said mammal to preferentially target said oligonucleotide to said liver cells in said mammal to modulate the expression of a gene in said liver cells wherein said oligonucleotide is cleared from the circulation at approximately the same rate as a second oligonucleotide wherein said second oligonucleotide has no sterol moieties covalently bonded thereto...

- 7. (Original) The method of claim 6, wherein said liver cells are endothetial cells.
- 8. (Canceled)
- 9. (Original) The method of claim 6, wherein at least one of said sterol moieties is a cholesteryl moiety.
- (Original) The method of claim 6, wherein said oligonucleotide comprises two cholesteryl moieties.
- 11. (Original) The method of claim 6, wherein said sterol moieties are bound at the 2'-O, 3'-O or 5'-O positions of said oligonucleotide.
- 12. (Currently amended) A method of treating a mammal an animal-having a hepatic disease or disorder associated with a protein encoded by a gene, comprising the step of: administering to said mammal an antisense oligonucleotide which hybridizes to said gene,

wherein said oligonucleotide has at least two sterol moieties covalently bonded thereto.

Attorney Docket No.:

ISIS-5028

Serial No.:

10/080,979

Page 4

13. (Canceled)

- 14. (Original) The method of claim 12, wherein at least one of said sterol moieties is a cholesteryl moiety.
- 15. (Original) The method of claim 12, wherein said oligonucleotide comprises two cholesteryl moieties.
- 16. (Original) The method of claim 12, wherein said sterol moieties are bound at the 2'-O, 3'-O or 5'-O positions of said oligonucleotide.

17-22. (Canceled)